APOPTOSIS

The concept of programmed cell death, or apoptosis, has exploded into a major scientific field of interest for cell biologists, oncologists, and many other biomedical researchers. Apoptosis occurs throughout the lifetime of most multicellular organisms. During development, for example, the selective death of cells is vital to remove tissue between the digits to produce fingers and toes. Apoptosis is also necessary to destroy cells that represent a threat to the integrity of the organism, for example, cells infected by a virus. In many cancers the genes regulating apoptosis are defective, producing immortal, continuously proliferating cells. This book discusses the philosophical and technical difficulties in defining the moment of death for a cell, as well as the biological implications and significance of programmed cell death. Recent developments in the genetic control and interacting gene networks associated with apoptosis are presented. The book is written for advanced undergraduate and postgraduate students, and is highly illustrated to aid understanding.

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THE LIFE AND DEATH OF CELLS

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CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town,
Singapore, São Paulo, Delhi, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521626798

First published 2004
Reprinted 2005

A catalogue record for this publication is available from the British Library

ISBN 978-0-521-62271-4 Hardback
ISBN 978-0-521-62679-8 Paperback

In memory of Sarah

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Preface

The death of cells in tissues and organisms was recognised by nineteenth-century histologists and anatomists, particularly those from Germany. On the whole it was regarded as a relatively unimportant process; an entirely passive phenomenon that occurred as a consequence of individual cells sustaining damage or becoming senescent and dying. This view remained unchanged for more than a century until it was realised that the death of cells in a tissue was part of the counterbalance to cell division in determining the overall rate of growth of the tissue. This came to prominence in studies on the growth of tumours, particularly from the work of Gordon Steel, where cell loss was realised, in addition to cell proliferation, to be important in contributing to the overall rate of tumour growth. There are two major elements that counterbalance proliferation. First, there is loss of proliferating cells to a functionally differentiated state with no capacity to return to a proliferative state. Second, there is loss of cells through cell death. Dead cells were recognised in sections of tumours analysed through the microscope in a way that was similar to that described in the early literature. For a time, the concept of cell death as an important factor in growth rate remained the almost exclusive preserve of those working on questions relating to tumour growth. From the early days of microscopic analysis, researchers of the embryological development of organisms from worms and flies to humans, and those studying metamorphosis in the life cycle of organisms such as butterflies and frogs, realised that the loss or the removal of cells was a vitally important phenomenon: this process of cell removal was termed *programmed cell death*.

In 1972, a group of pathologists from Aberdeen and Brisbane published a research paper that radically changed the field of research into the processes of cell death. In this paper, they described in detail the changes that occurred in the electron microscopic appearance of individual cells when they died: in this case, the death of kidney tubule cells in response to high levels of a corticosteroid. This and subsequent studies clearly indicated that, far from being a passive phenomenon, cell death could involve considerable cellular activity. The term *apoptosis* was coined to describe this process of cell death, with active cellular involvement implying a suicide-like process was programmed into cells. There was initial reluctance by the more conservative elements of the scientific community to accept the phenomenon of apoptosis, and for a while programmed cell death, as described by developmental biologists, and apoptosis were thought of as separate processes. Inevitably though, these have now been seen to be essentially the same active process, and since the mid-1980s apoptosis research has flourished into an exponentially expanding field. Surprisingly, it was work in the United Kingdom and Australia that kept the concept of apoptosis alive in the late 1970s and early 1980s. It was only after this that the American scientists entered the field.

It is now recognised that cells may die because they become old and defective, because they are surplus to the requirements of the tissue, or because they incur some damage. Each of these possibilities involves considerable internal cellular programming to regulate gene and protein expression. In addition to internally derived signals, cells can be instructed to commit suicide in response to external signals from their direct neighbours or local cells, from cells of the immune system, and from systemically derived signals.

Apoptosis is an integral part of the regulation of tissue morphogenesis during development and also the regulation of cell production under the stable conditions that one sees in adult organisms in species as diverse as worms, flies, mice, and humans. Abnormalities of tissue growth (e.g., shrinkage or atrophy of tissues with ageing, and diseases of increased proliferation like psoriasis and abnormal

growth like cancer) may all result from an imbalance between the processes of cell division and cell loss by differentiation and apoptosis. Extensive studies are currently underway to determine the molecular and genetic regulation of apoptosis in a variety of situations. Such studies may help in understanding and ultimately preventing the development of tumours and other diseases of proliferation. They may facilitate also the development of entirely new strategies for treating such diseases.

With the evolution and expansion of research into apoptosis, it is becoming an important discipline within the field of cell biology. I have attempted here to describe in simple terms the current status of our knowledge of apoptosis, to explain some background to the field, and to describe some of the difficulties and uncertainties that surround experiments involving apoptosis and the attempts to assess quantitatively the number of cells dying in various circumstances. I have not included extensive lists of references, which clutter and distract from reading the text, but have included various lists of additional reading matter, which generally are either key papers or extensive review articles from which further papers may be identified.

Most of the conclusions that one draws in scientific research represent approximations to the truth. This is particularly true of the field of apoptosis research as it stands at the moment. The search for the truth is, in my view, not particularly facilitated by some of the modern techniques of molecular biology, which commonly are performed on highly specialised cell culture systems and often make use of unconvincing changes in the intensity of blots and gels and make little use of statistical approaches for testing for significance. In apoptosis research, the work can often be based on single or a small number of experiments, the results of which are rarely, if ever, of the 'all or none' type.

It is relatively easy to identify cells that are dying in tissues, but to define the moment at which cell death starts and finishes is extremely difficult. The problems of defining life and death for a cell are similar to the current medical and ethical difficulties associated with defining life and death in humans. Furthermore, the number of cells that one

sees displaying the characteristics of dead cells in a tissue may not be the same thing as the number of cells dying per unit of time, for a variety of complex reasons.

I have been involved in apoptosis research since the mid-1970s and my interests have centred on the role played by apoptosis in a rapidly dividing tissue: the intestinal mucosa. This is probably one of the most extensively studied tissues and provides a nice model biological system for studying cellular interactions. I shall refer to it fairly heavily and because it is a tissue with which I am very familiar it will, inevitably, be something of a personal and idiosyncratic view that is presented.

I have also attempted to explore some of the difficulties outlined above, which on the whole have not been addressed by current researchers. I do this to emphasise the point that nothing is entirely clear and conclusively resolved in science, in the hope that it may stimulate new, young scientists to attempt to address some of the questions and clarify the uncertainties, and so approach closer to the scientific truth. I also hope that some may become interested in understanding the complex biochemical interactions and intercellular dialogues that go on between cells in the body that determine whether they divide, differentiate, or die.

C.S.P.

Note: A good background review on apoptosis can be found in Harmon, B. V., and Allan, D. J., Apoptosis: a 20th century scientific revolution. In: *Apoptosis in Normal Development and Cancer*. Taylor & Francis. London, 1–19, 1996.

Acknowledgements and dedications

I have been thinking of setting down a personal view of the topic of apoptosis for some time and I am grateful to Cambridge University Press for giving me the opportunity to do so.

I would like to thank my friend and colleague Professor Aldo Beccioloini for providing me with a desk, some peace and quiet, a beautiful climate, and a cultural, gastronomic, and oenologistic environment in Florence, in which I was able to put together many of these chapters whilst a visiting professor over several years. Dr. Manuela Balzi has also always been an invaluable friend and assistant while I have been in Florence.

I should also like to thank Professor John Kerr and his colleagues, particularly Jeffrey Searle, Brian Harmon, and David Allan, for introducing me to the topic of apoptosis in the early seventies and inviting me to stay in Brisbaine as a visiting professor some years ago.

Throughout my scientific career at the Paterson Institute for Cancer Research, I have been supported by long-term grants and a life fellowship from the Cancer Research Campaign (now Cancer Research UK), to whom I am extremely grateful.

I am grateful to Christine Sutcliffe for her help over the past few years in preparing many documents and reports for a largely computer-illiterate scientist.

A book like this would not be possible without many years of work in the field, during which I have relied on the hard work of a large number of dedicated and loyal staff and visiting scientists performing the necessary experimental work. These are too many to list but I make an exception for my long-suffering research assistants,

Caroline Chadwick, who worked with me for more than twenty years, and Dawn Booth, for her highly professional approach and help. I also want to acknowledge Dr. Cath Booth for her friendship, help, and continuous good humour during the various highs and lows of academic grant-funded research. It is to Caroline, Cath, and Dawn and to all the friends and colleagues who have supported me over the years that I dedicate this book. I would also like to acknowledge the love, great help, and support of Ed, Steve, and Mike over the past few difficult years.

C.S.P.